ENDOTHELIAL PHAGOCYTES IN PLEURAL EXUDATE DUE TO THE BACILLUS TYPHOSUS.

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(From the William Pepper Laboratory of Clinical Medicine.)

The important part played by phagocytic endothelial cells in the pathology of typhoid fever has been recognized since Mallory,[1] in 1898, after a careful histological study of a large mass of material, came to the conclusion[2] that "the typhoid bacillus produces a mild type of inflammatory reaction consisting almost entirely of endothelial leukocytes which accumulate in large numbers where the typhoid toxin is strongest and thus form the lesions characteristic of typhoid fever. These endothelial leukocytes are strongly phagocytic for other cells, incorporating and digesting large numbers of them. In the intestinal lesions they take up chiefly lymphocytes, in the spleen, red blood-corpuscles, and in the blood-vessels, especially of the portal circulation, polymorphonuclear leukocytes and red blood-corpuscles." These endothelial phagocytes were demonstrable not only in the lymph nodules of the Peyer's patches and of the spleen, but also in the mesenteric lymph nodes, the liver, bone-marrow, clotted blood in the heart and in the alveolar exudate of pneumonia complicating typhoid fever. Mallory, moreover, quotes Eichhorst as having seen similar cells in the blood drawn from the tip of the finger of a typhoid patient during the second week of the disease. In all the localities mentioned the phagocytic cells have the same size and appearance while the engulfed cells vary in type according to the locality. The endothelial phagocytes are uniformly large, with more or less round, lightly staining, eccentrically placed nuclei, and a protoplasm which stains with varying intensity. The formation of phagocytic cells by proliferation from endothelial cells was not claimed by Mallory to be peculiar to typhoid except in regard to location, extent, and degree. He believes that their formation in large numbers may be the result of any mild toxin which acts diffusely and causes proliferation and not necrosis. Under these conditions it is clear that there is a close relationship histologically between tuberculosis and the typhoid process, and this becomes of considerable diagnostic interest when the reactions to infection of a serous surface, such as the pleura, are studied.

The pleura is covered throughout by a single layer of endothelial cells, and these cells appear in small numbers and are readily

[1] Jour. Exp. Med., 1898, iii, 611.

[2] Mallory, F. B., Principles of Pathological Histology, 1914, p. 165.

recognized in stained preparations of the sediment from almost all collections of fluid in the pleural cavity. By some they are referred to as endothelial cells and by others as large mononuclears, and it is claimed that similar forms may arise from connective-tissue cells, from the perivascular lymph spaces, or from the blood stream. They resemble very closely the endothelial phagocytes which proliferate in various localities in typhoid fever.

In mechanical effusions the endothelial cells are seldom numerous, but often occur in groups of two or more. Such groups are spoken of by the French writers as "placards" or placques, and have long been considered as indicating a mechanical or non-inflammatory effusion. Widal, Ravaut, and Dopter,[3] in 1902, emphasized the fact that in a mechanical effusion the endothelial cells are desquamated in groups and remain joined together and typical in appearance, while in an infectious pleurisy with effusion the endothelial cells may at first be joined in placques, but they soon separate and then become markedly altered in appearance. Thus they become swollen and stain poorly, vacuoles appear in the protoplasm, and the cell outline becomes indistinct. Also, it is only after the cell masses separate into single cells that they may exhibit phagocytic properties. This, however, is unusual in mechanical effusions. In all pleural effusions due to organisms other than the typhoid or tubercle bacillus the endothelial cells play but a small part and are usually lost sight of in the great polymorphonuclear reaction.

When the tubercle bacillus is the etiological factor the pleural effusion might be expected to show in stained preparations at least a moderate number of endothelial cells and lymphocytes. Some observers, however, claim that while numerous endothelial cells may be present early in a tuberculous effusion, yet once the pleura becomes covered by a fibrinous membrane this variety of cell will cease to be found, and lymphocytes will become the sole or at least the predominating form. As a result of this the finding of endothelial cells in an effusion of some duration has been considered as a strong argument against the effusion being of tuberculous origin, and Naunyn goes so far as to state that the presence of endothelial cells excludes tuberculosis. On the other hand, Koster[4] found endothelial cells in the effusion of almost 50 per cent. of the known cases of tuberculosis he investigated, and other observers corroborate this. In no case, however, has the endothelial cell been described as the predominating form, nor is phagocytosis mentioned.

Typhoid pleurisy is not common (an incidence of about 1 to 2 per cent., in large series of reported cases), and there are but a few records of the cytology of effusion due to this infection. The cases reported indicate considerable variation in the cell picture.

[3] Compt. rend. d. l. Soc. de biol., 1902, liv, 1005.
[4] Nord. Med. Ark., 1905, xxxviii, II, 3, p. 1.

Widal and Ravaut,[5] to whom we owe the first systematic study of cytodiagnosis in puncture fluids, state that typhoid pleurisies are often hemorrhagic and contain a relative abundance of large mononuclear cells. Vincent[6] in each of two cases of pleurisy in typhoid fever, found that the effusion, although purulent, contained a considerable number of endothelial cells. He makes no mention of phagocytosis nor did cultures show the Bacillus typhosus; on the other hand, one effusion produced tuberculosis when injected into a guinea-pig. Widal and Lemierre[7] report a case in which endothelial cells predominated in the effusion. Some of these cells were vacuolated and of very large size, but no mention is made of phagocytosis. In this case the effusion yielded the typhoid bacillus on culture and also a positive agglutination test for the typhoid bacillus. The pleural effusion observed by Levi[8] in the course of typhoid fever, was sterile, but contained numerous polymorphonuclear cells and a moderate number of large mononuclears. Phagocytosis is not mentioned. Earl[9] states that the typhoid bacillus calls forth a polymorphonuclear excess of from 50 to 80 per cent. of the cells of an effusion.

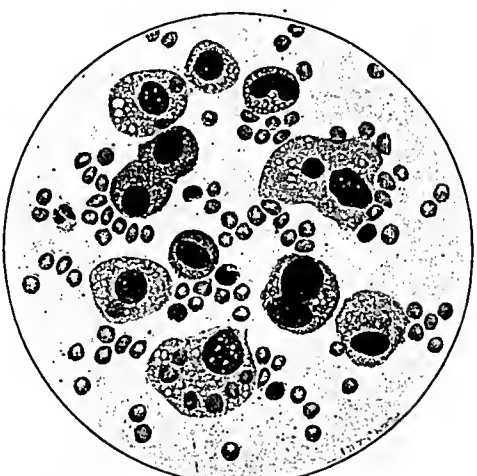
The variations in these findings are probably to be explained by the fact that, clinically, typhoid pleurisy appears in two more or less distinct forms, and also that the effusions studied were obtained at different stages of the process. Pleurisy may complicate the onset of typhoid fever, and this is the form which has led to the use of the term pleurotyphoid by the French. The pleuritic symptoms may be marked but little or no effusion develops, and the whole process usually disappears after a few days. On the other hand, pleurisy may develop late in the disease at the time when purulent complications commonly occur. This form goes rapidly on to empyema, and is comparable in every way to the other purulent complications of the disease. The cells in such purulent collections are almost wholly polymorphonuclears, and a pyogenic coccus is sometimes obtained upon culture either alone or with the Bacillus typhosus. It is impossible to say whether in these purulent effusions the polymorphonuclear reaction is to be attributed to a greater intensity or concentration of the typhoid toxin or to a superadded pyogenic infection.

In the transitory pleurisies occurring early in the course of typhoid fever the typhoid toxin is apparently not present in any great concentration, and one would expect in view of Mallory's work to find that the cells of the effusion were mostly of endothelial origin. Further, it might be expected that these endothelial cells would show active phagocytosis of other cells in the pleural effusion

[5] Compt. rend. d. l. Soc. de biol., 1900, liii, 648.
[6] Semaine méd., 1903, s. 370.
[7] Ibid., 1913, s. 385.
[8] Ibid., 1903, s. 370.
[9] Dublin Jour. Med. Sci., 1903, cxvi, 409.

just as do the endothelial leukocytes arising in other parts of the body in response to the typhoid infection. A careful search of the literature, however, does not reveal any record of such a finding, and the present example of endothelial phagocytosis in pleural exudate due to the Bacillus typhosus is therefore reported.

CASE.—The patient, an adult male, with no previous medical history, entered the hospital of the University of Pennsylvania, stating that he had been ill with fever and chills for three weeks. He complained of no localizing symptoms, but upon questioning admitted the presence of a slight pain in the chest for a day or two.



Endothelial phagocytes from pleural effusion due to Bacillus typhosus.

The temperature and pulse were elevated. Physical examination revealed nothing abnormal other than the signs of a small effusion at the base of the right lung. Upon aspiration a few cubic centimeters of hemorrhagic serous fluid were withdrawn, and from the cytology of this a diagnosis of pleurisy due to the typhoid bacillus was ventured. This diagnosis was promptly verified by finding that both the blood serum and the effusion gave a positive agglutination test with typhoid bacilli and later by obtaining the Bacillus typhosus in pure culture from both the blood and the effusion. The titre of agglutination was 1 to 1000 in the blood, and 1 to 800 in the effusion. A second aspiration several days later gave

similar fluid, but all signs of effusion then disappeared and no fluid was obtained on a third thoracentesis. The patient ran a typical typhoid course, without complications, to complete recovery, and at no time could any evidence of pulmonary disease be found either by physical examination or by stereoscopic roentgenographs.

The fluid obtained by aspiration was distinctly hemorrhagic but did not clot upon standing. Spreads made from the sediment and stained with Wright's stain showed the unusual cytology which is well illustrated in the accompanying drawing of selected cells. Excluding erythrocytes, about 60 per cent. of the cells of the effusion were large mononuclear cells with more or less round nuclei which were usually placed eccentrically and did not stain as deeply as did the nucleus of the small lymphocyte. The protoplasm of these large mononuclear cells varied in appearance; sometimes it was stained uniformly and deeply, while in other instances it was vacuolated and stained palely. In every respect these cells resembled the endothelial leukocytes or macrophages described by Mallory. A moderate number showed phagocytosis and had engulfed one or more erythrocytes. Several had engulfed lymphocytes and one instance of phagocytosis of a polymorphonuclear cell was observed. Some of the cells ingested showed evidence of digestion, while others appeared unaltered. Occasionally the endothelial cells were grouped together in plaques and these cells never showed phagocytosis. Through many gradations these endothelial cells merged into the typical mononuclear of the circulating blood and it was impossible to draw any distinguishing line. The effusion contained these cells in great excess of the white-blood cell count of the circulating blood and a careful search of stained preparations of the latter failed to reveal any large endothelial cells or any phagocytosis by the usual mononuclears.

This observation of the endothelial character of the reaction of the pleura to the typhoid bacillus and of the phagocytic power of such cells in a pleural effusion is of interest not merely from its correlation of typhoid pleurisy to the general pathology of typhoid fever, as described by Mallory, but also from its possible diagnostic significance. In the case here reported the diagnosis was ventured with hesitation, but it would be warranted with greater confidence in the future upon finding a similar cytology. Pleurisy with effusion early in the course of typhoid fever is uncommon, but in any suspicious case an effusion should certainly have its cytology determined, if by this simple step a diagnosis may even occasionally be reached.

Conclusion. Pleurisy with effusion due to the Bacillus typhosus may occur early in the course of typhoid fever. The effusion is apt to be hemorrhagic and to contain a large number of endothelial leukocytes similar to those found elsewhere in the lesions of typhoid fever. These endothelial macrophages show phagocytosis of other cells, especially the erythrocytes of the effusion.